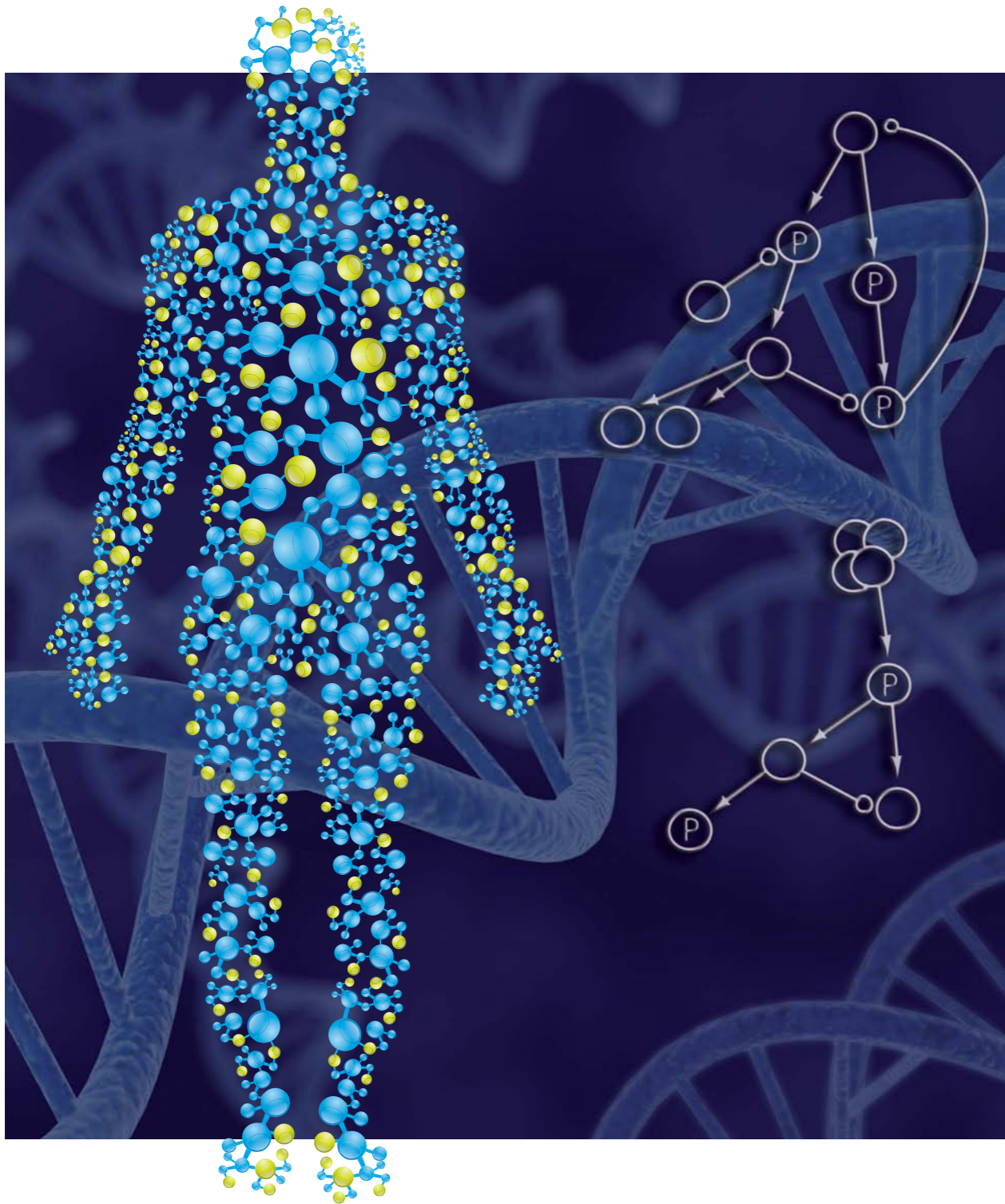# Decoding Network Dynamics in Cancer

ECCB-BioNetVisA
September 7th 2014
Strasbourg, FR

Rune Linding

Cellular Signal Integration Group (C-SIG)
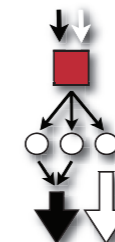Biotech Research & Innovation Centre (BRIC)
University of Copenhagen (UCPH)

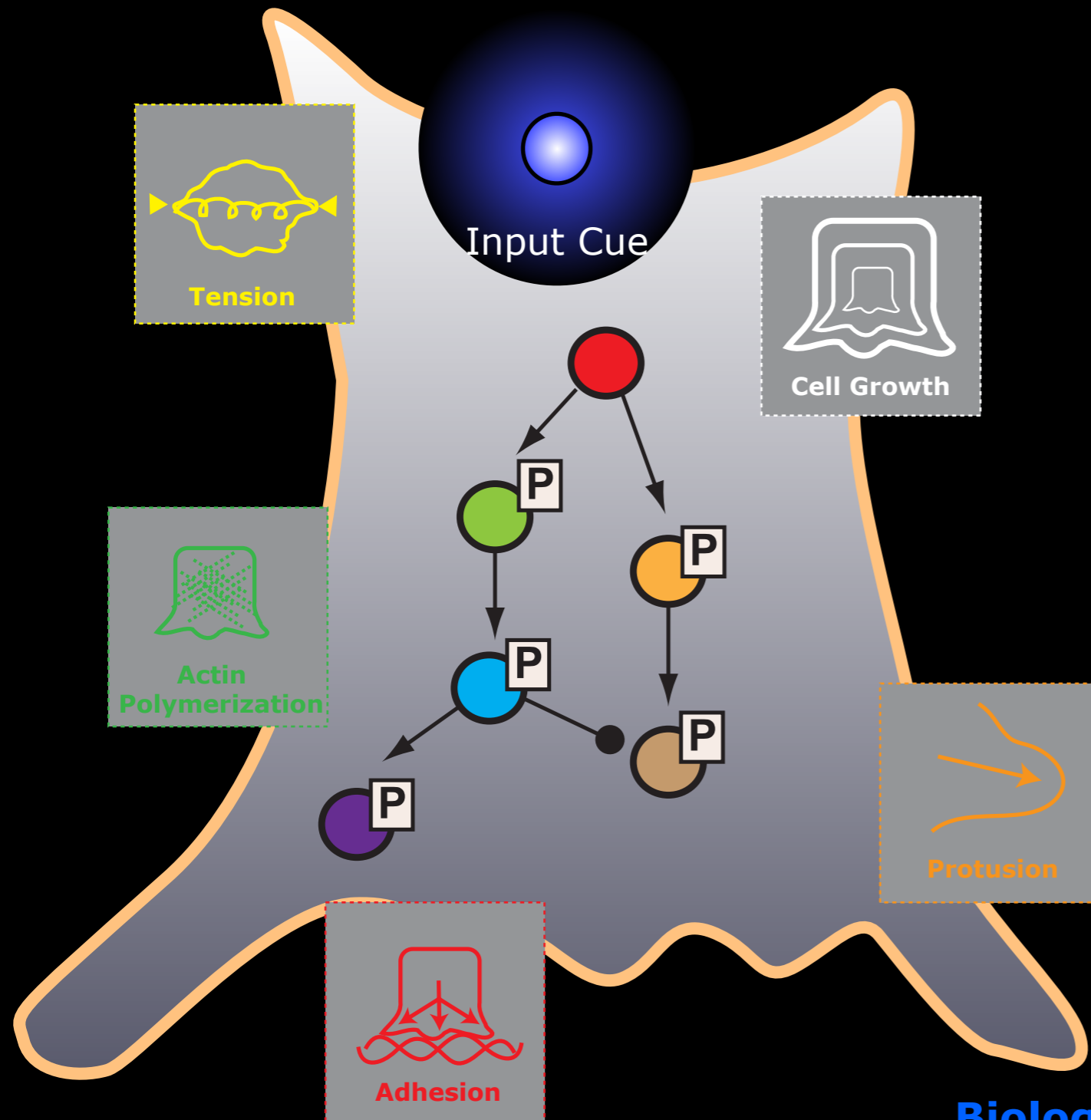**www.lindinglab.org**

UNIVERSITY OF COPENHAGEN

BRIC
Biotech Research & Innovation Centre

Cellular Signal Integration Group

Dynamic Signaling Networks integratively links genome & environment to phenotype

Tension

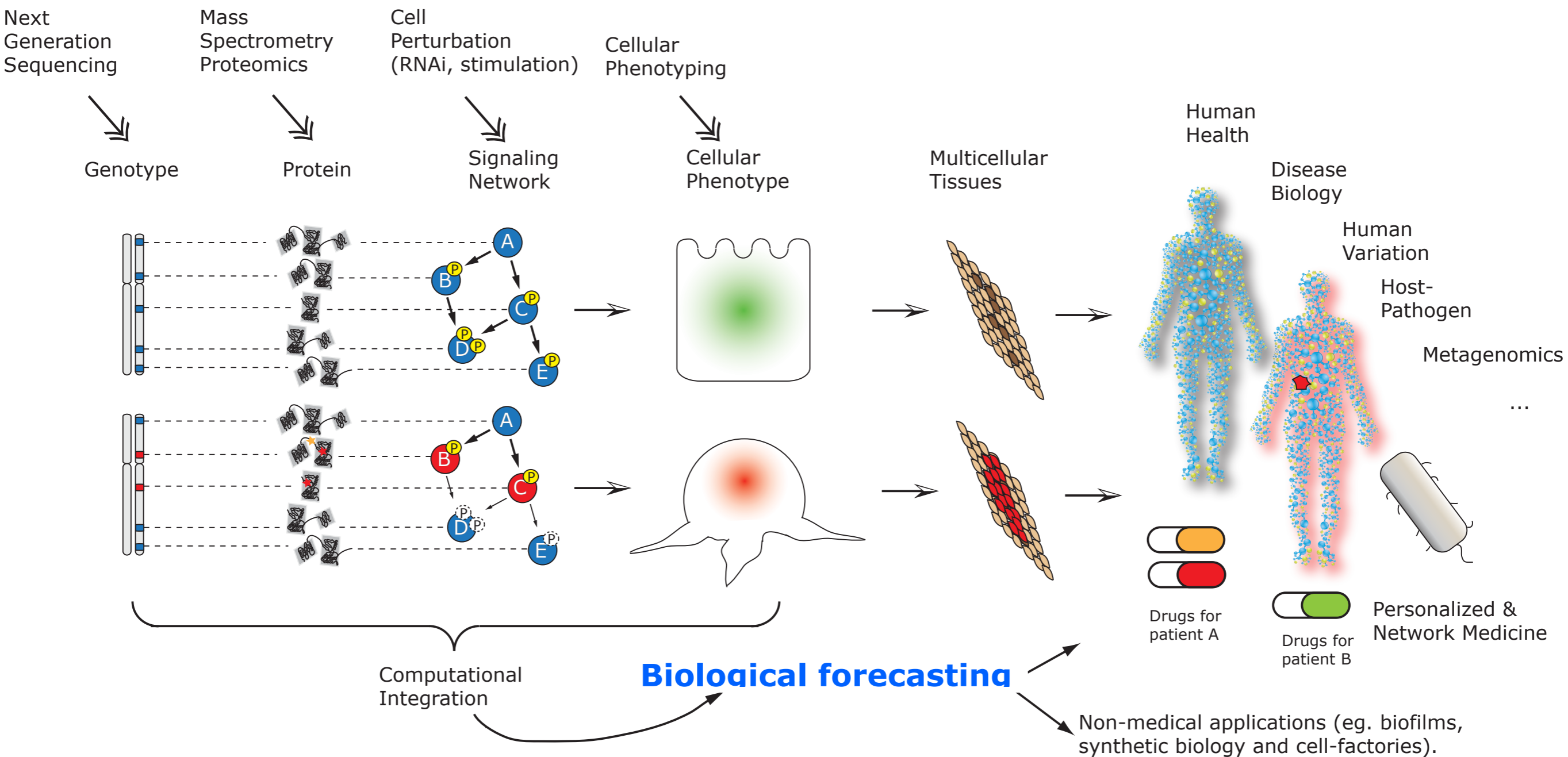Input Cue

Cell Growth

Actin Polymerization

Protusion

Adhesion

(1) Cell Behavior is Governed by Multivariate Network States

(2) Architecture and information flow of signaling networks drives phenotype

(3) Dynamics in signaling networks steer exploration of phenotypic landscapes/ spaces

(4) Complex diseases mediated by distorted dynamics/topologies in protein signaling networks (future drugs will target networks, "network medicine").
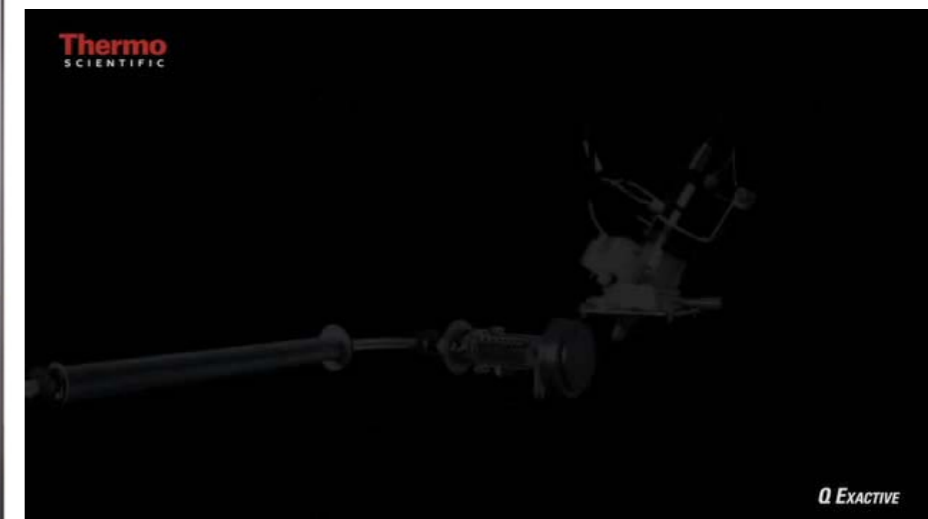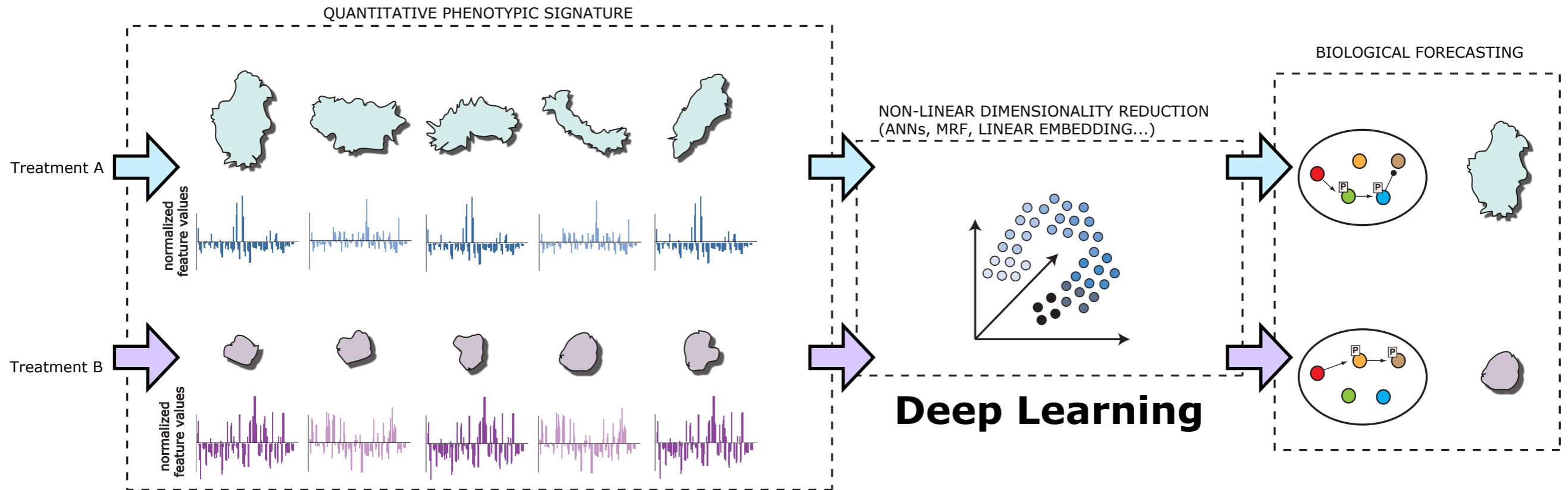
Biological forecasting

Cue ⟶ Signal ⟶ Response

Integrative Network Biology

Next Generation Sequencing

Mass Spectrometry Proteomics

Cell Perturbation (RNAi, stimulation)

Cellular Phenotyping

Genotype

Protein

Signaling Network

Cellular Phenotype

Multicellular Tissues

Human Health

Disease Biology

Human Variation

Host-Pathogen

Metagenomics

...

A
B
C
D
E

Computational Integration

Biological forecasting

Drugs for patient A

Drugs for patient B

Personalized & Network Medicine

Non-medical applications (eg. biofilms, synthetic biology and cell-factories).
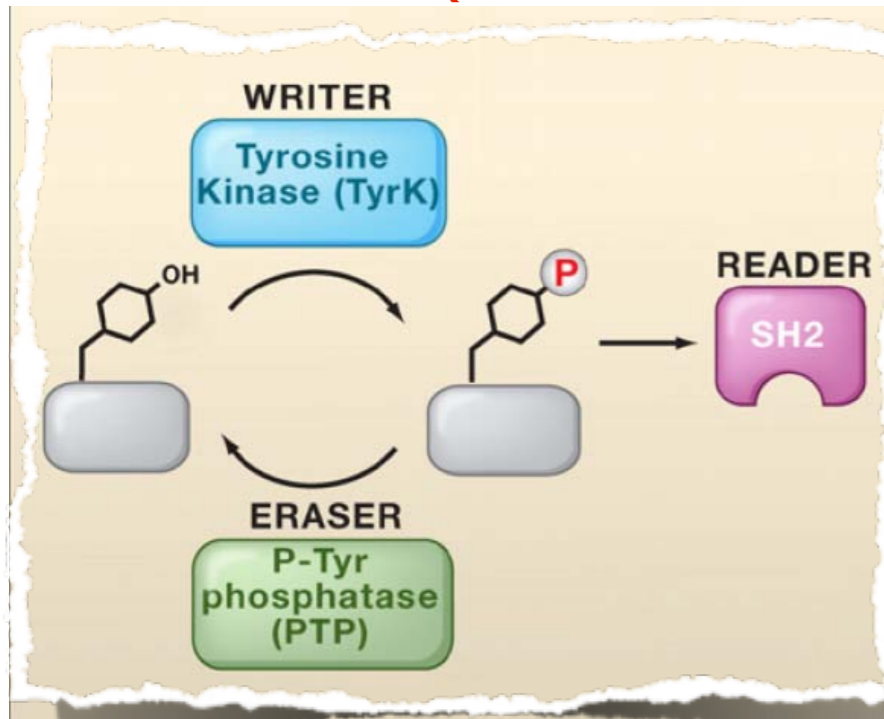
Biological Forecasting
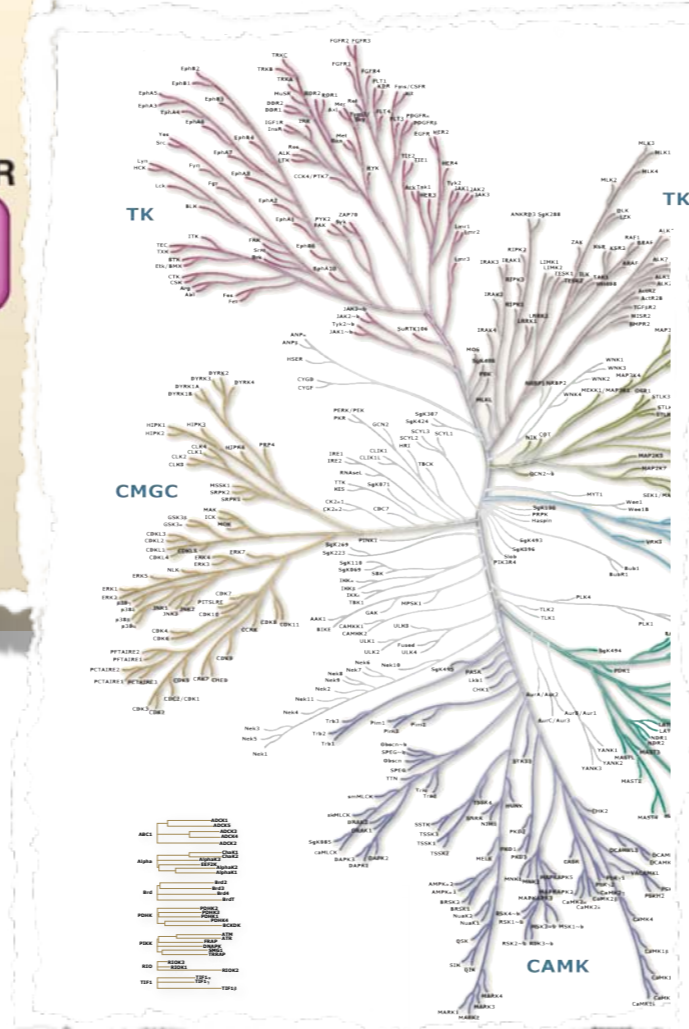# - Towards Global Prediction of Cell Behavior

Phosphorylation based cellular signal processing

The kinome (~540 kinases): A closed directional and dynamic regulatory system
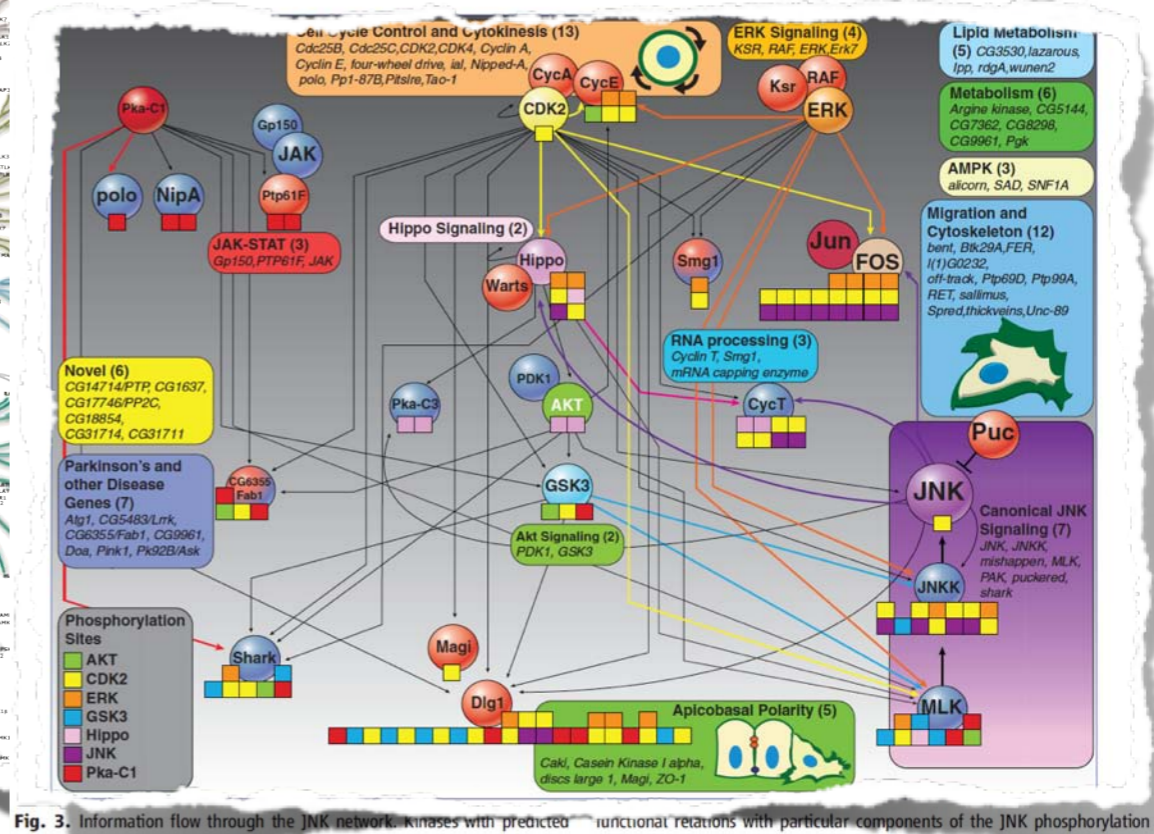

Lim and Pawson, Cell, 2010.

Manning et al. Science, 2002.

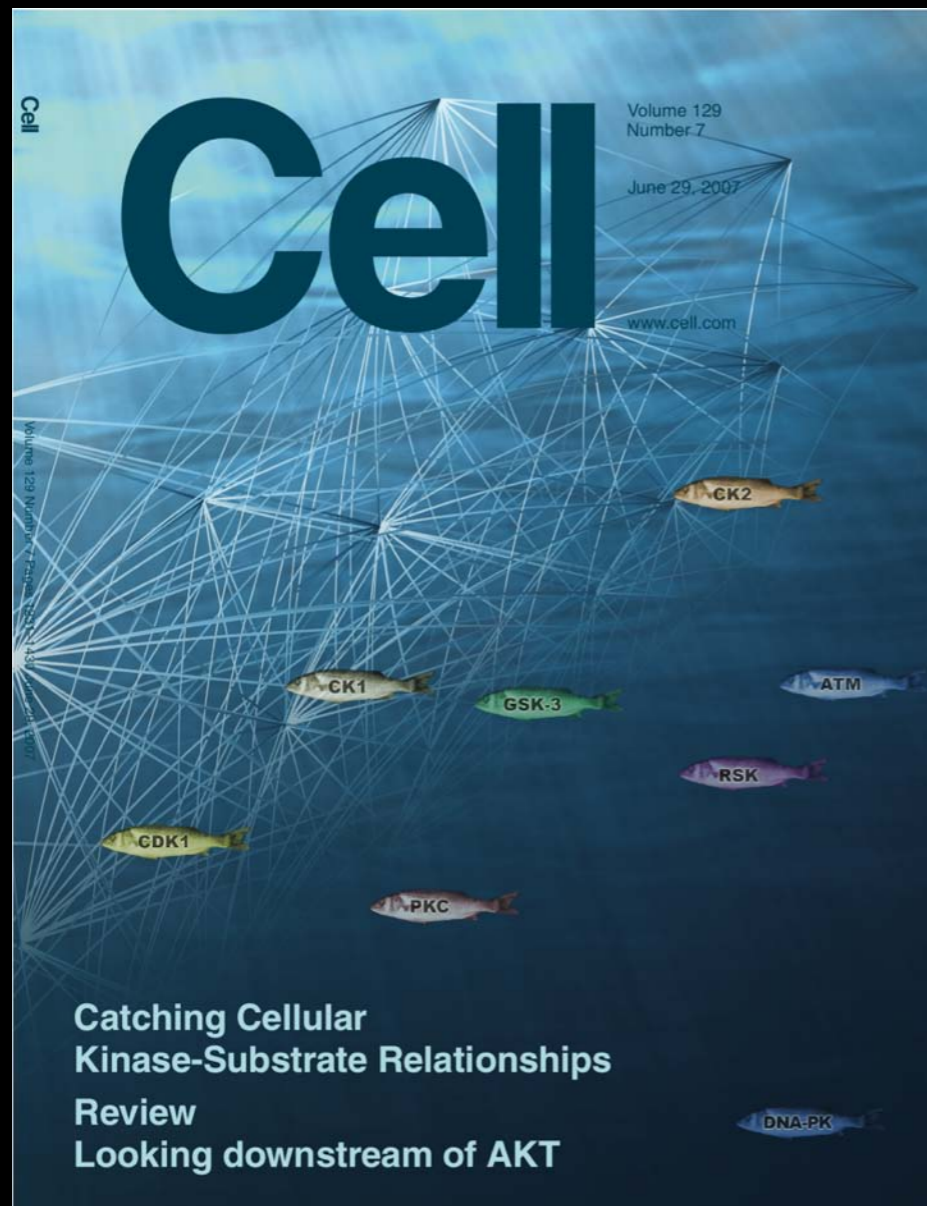Bakal, Linding, Llense et al. Science, 2008.

How does specificity emerge in these systems?

Motifs + Context

How do they evolve?

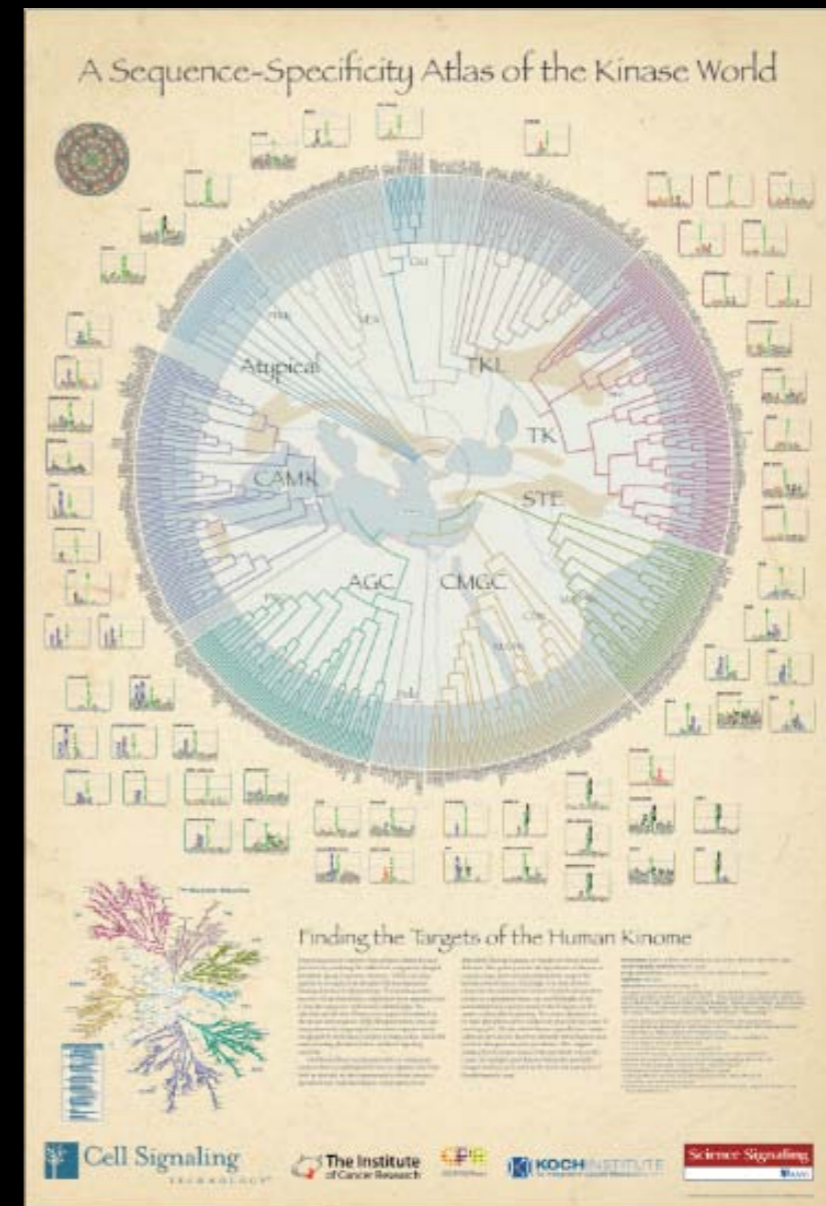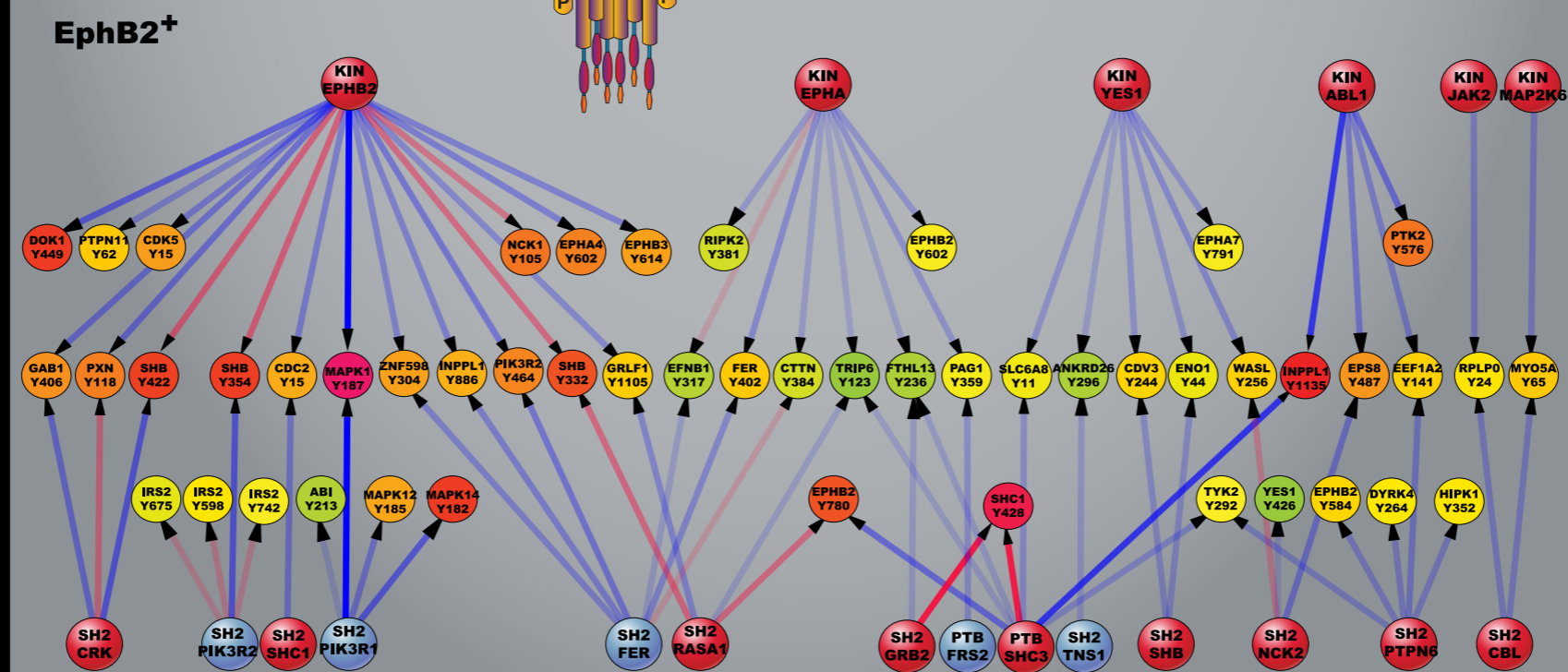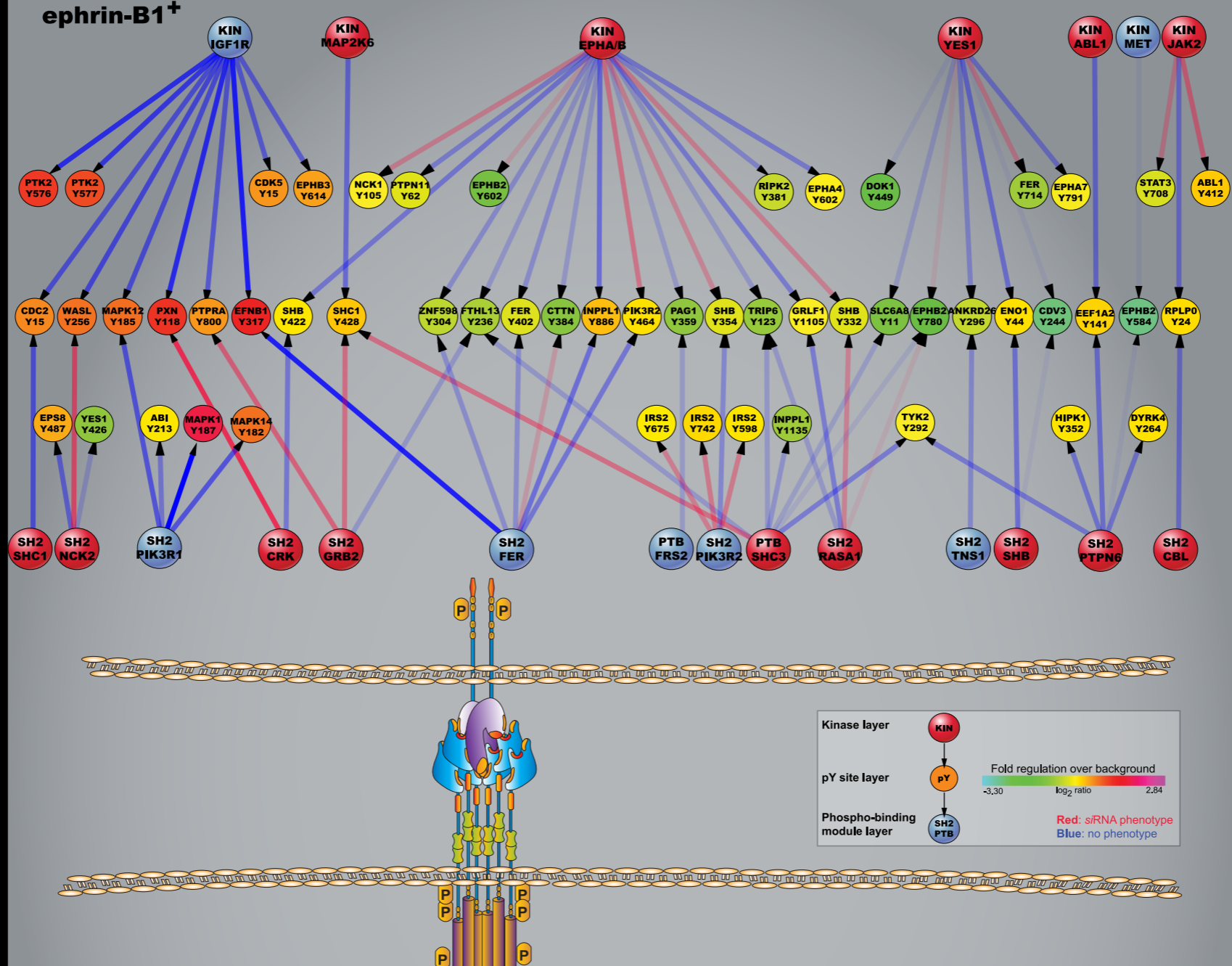**How do they become dysregulated?**

NetworKIN & NetPhorest Algorithms

Linding et al. Cell, 129, 2007.

http://NetworKIN.info

Miller et al. Science Signaling 2008 Sep 2;1(35):ra2.

http://NetPhorest.info

ephrin-B1+

EphB2+

Pawson &
Linding Labs
Science 2009.

KinomeXplorer
- Integrated Platform for Kinome Biology Studies

Horn, Schoof, Kim et al., Nature Methods, 2014.
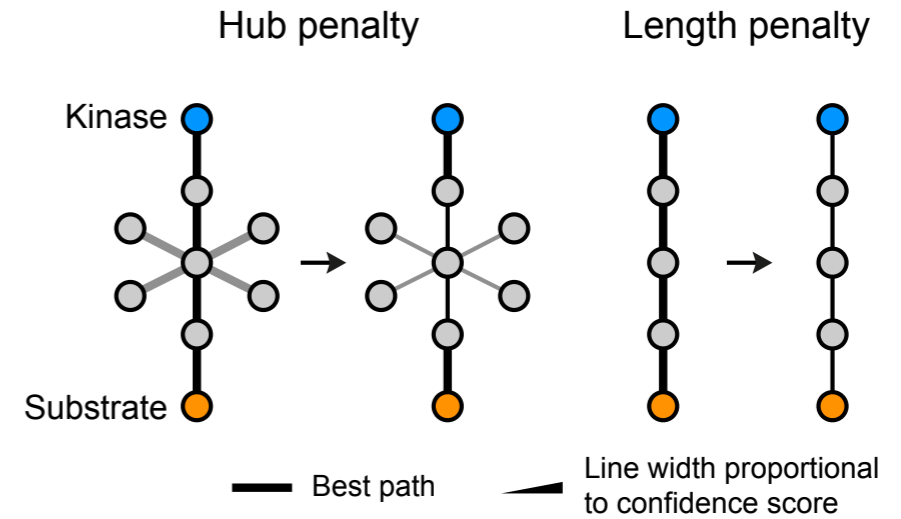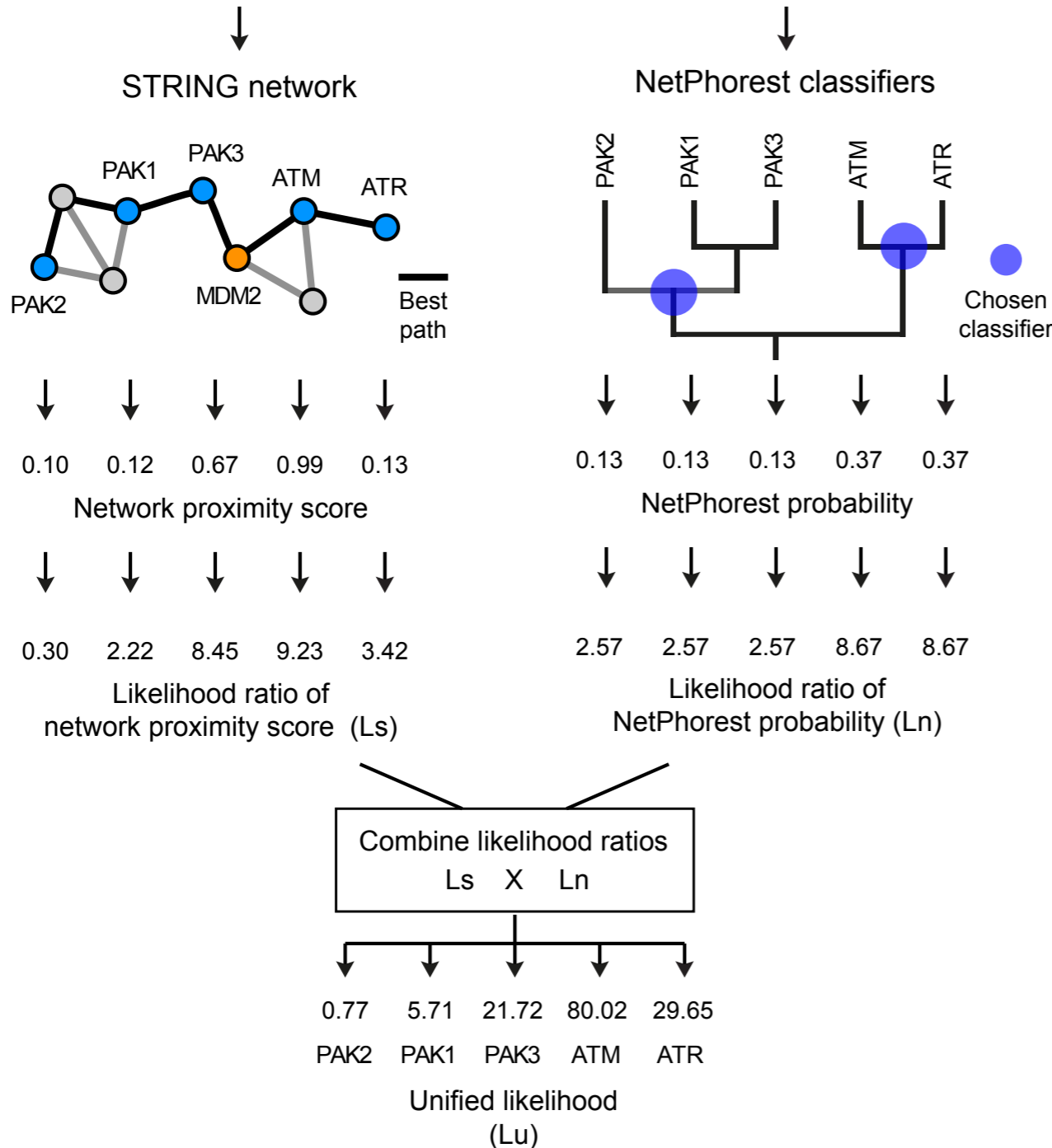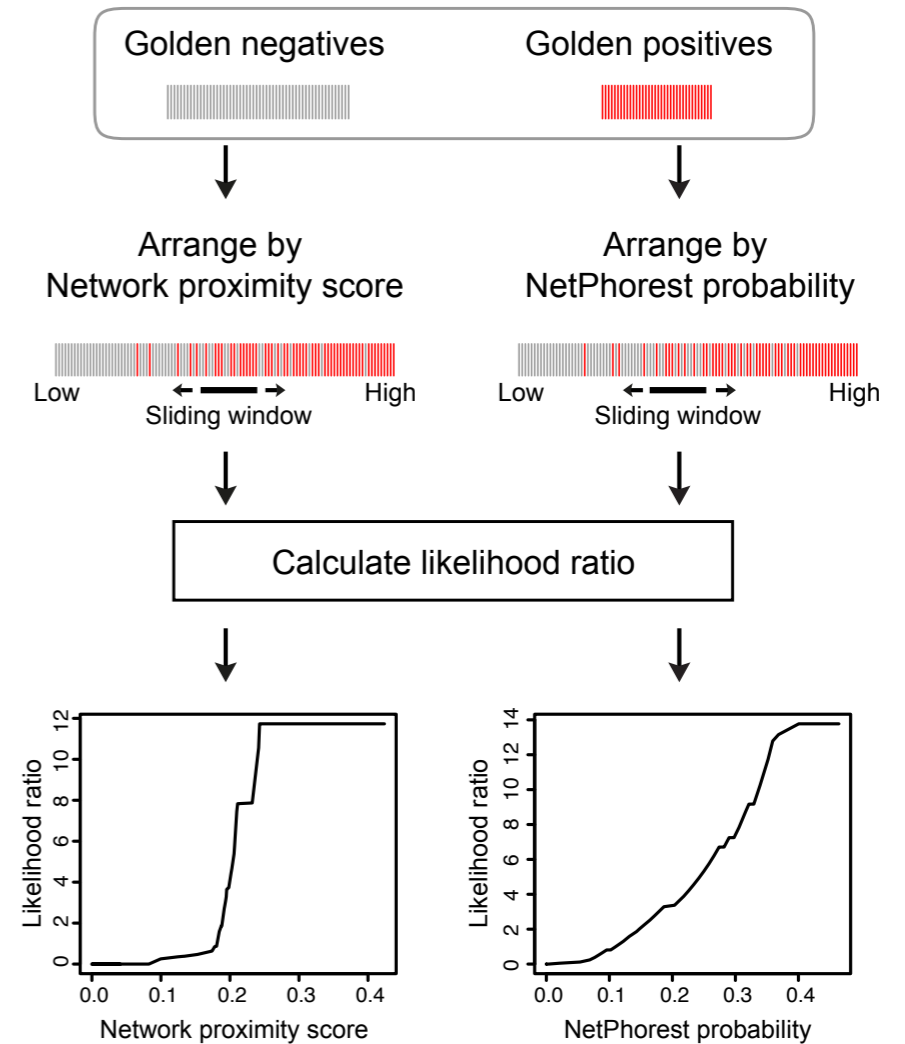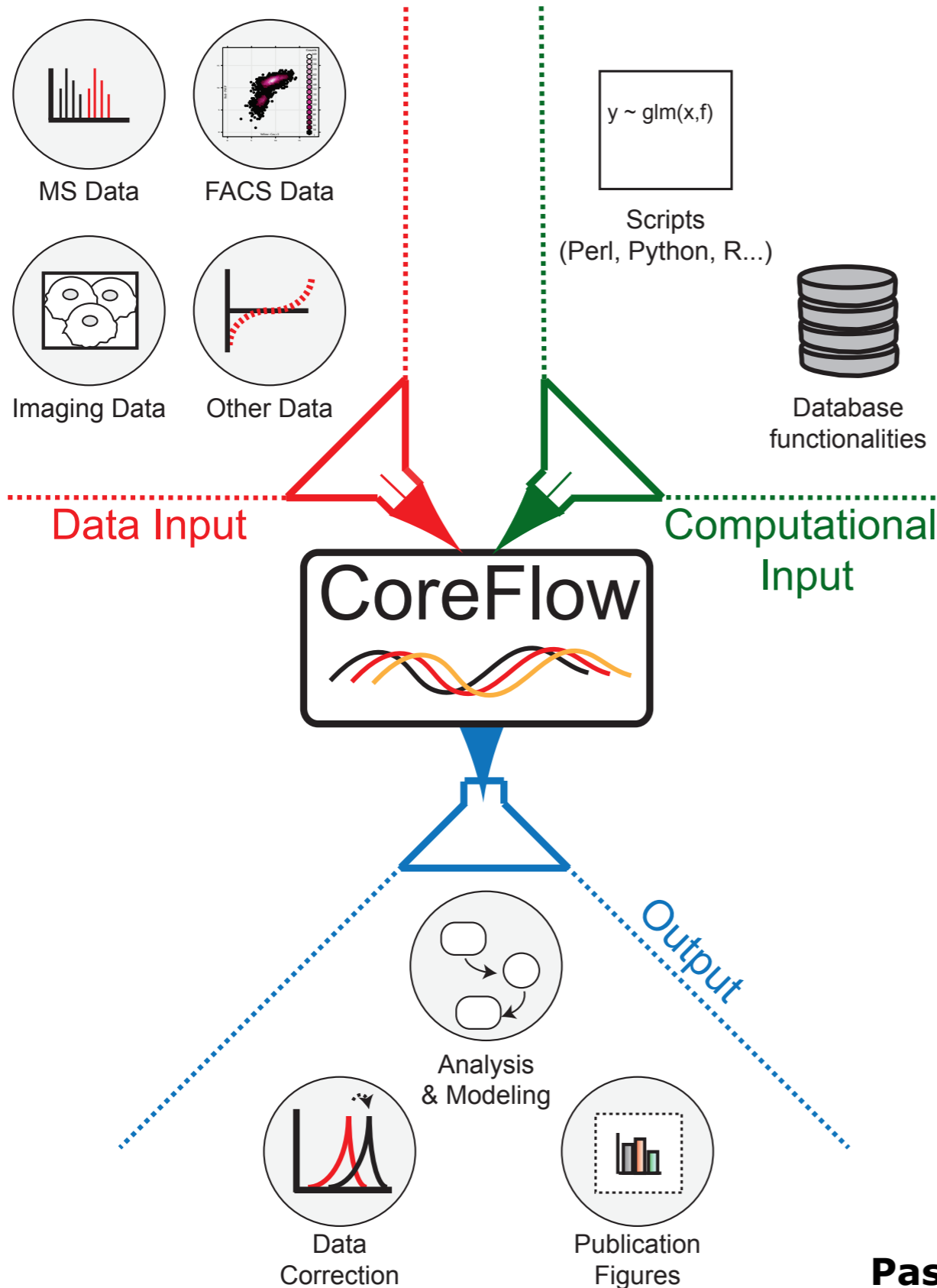
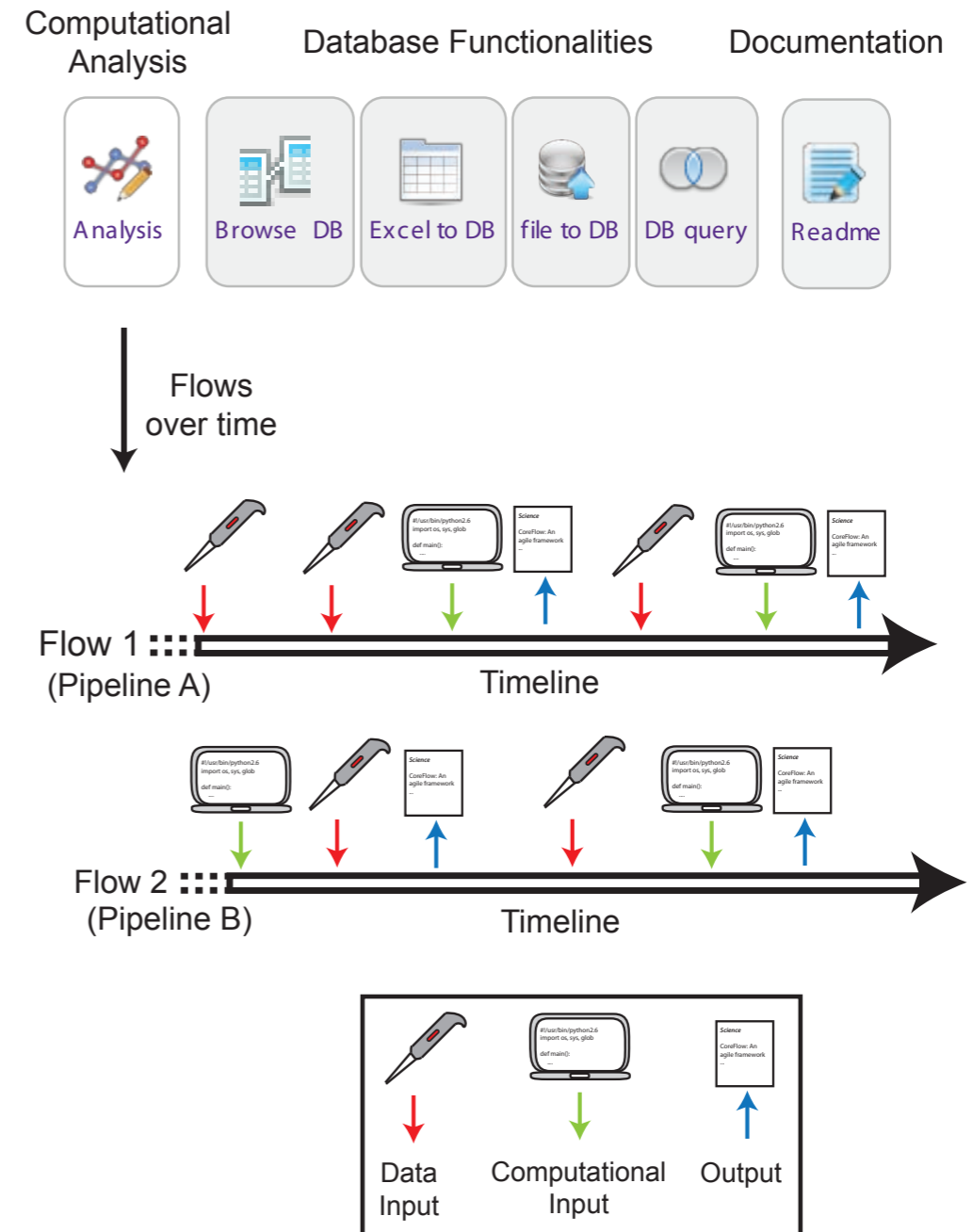# **CoreFlow:** Comprehensive, Automated, Analytical & Statistical Data Processing Pipeline

where to download Figure: Pasculescu_figures.pdf
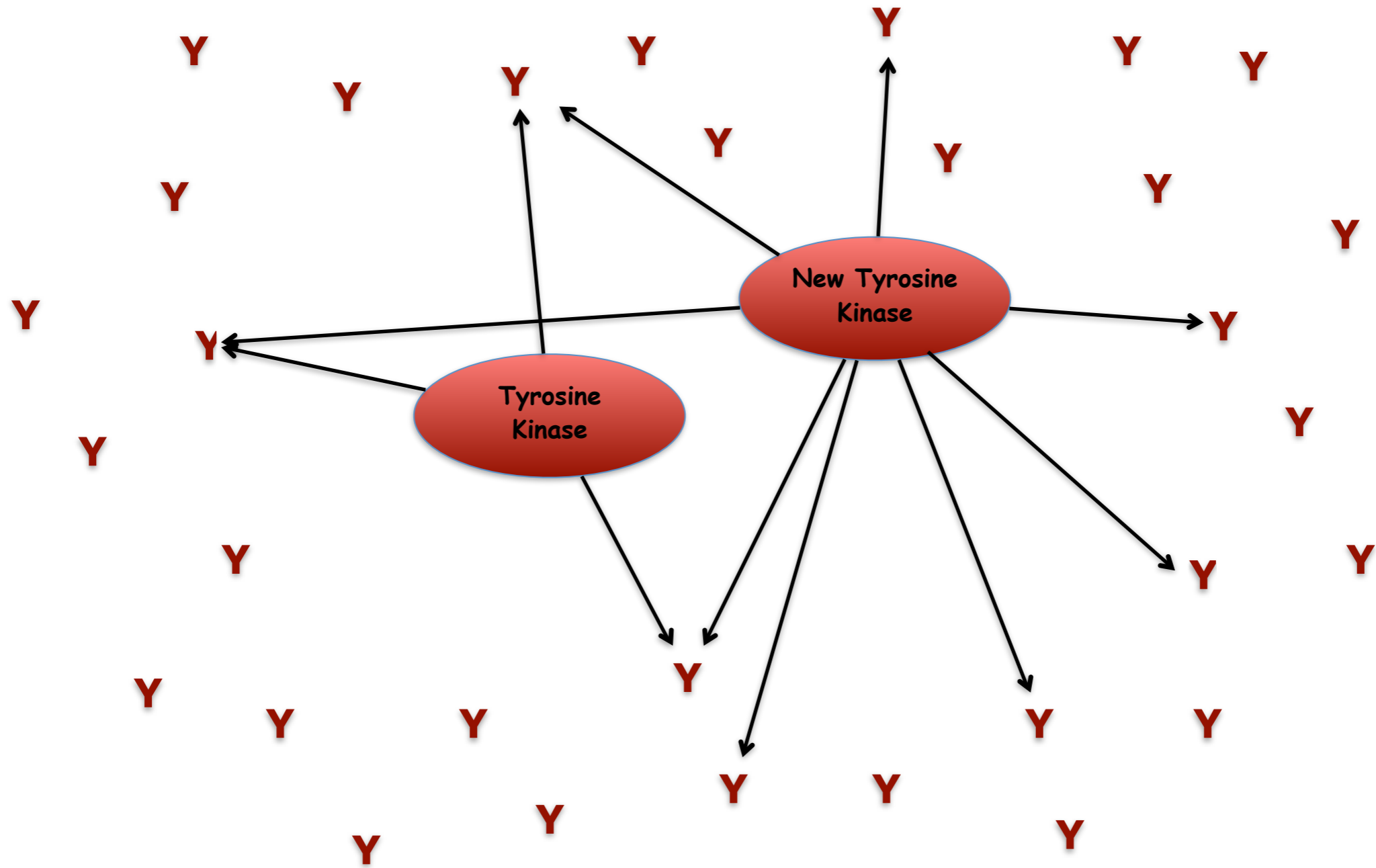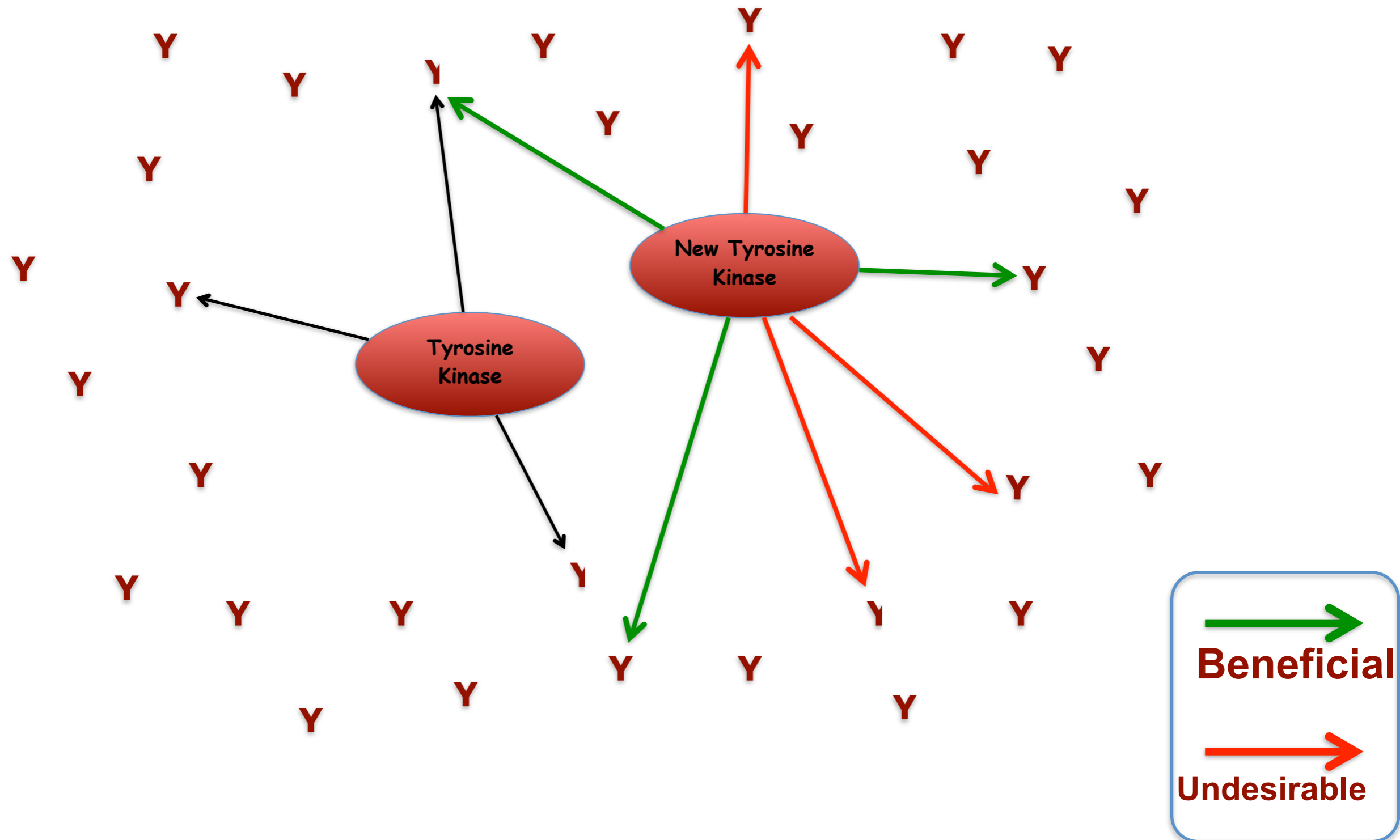
Pasculescu, Schoof, Creixell et al., J Prot Res 2014

Multi-cellularity & Noise in Tyrosine Signaling
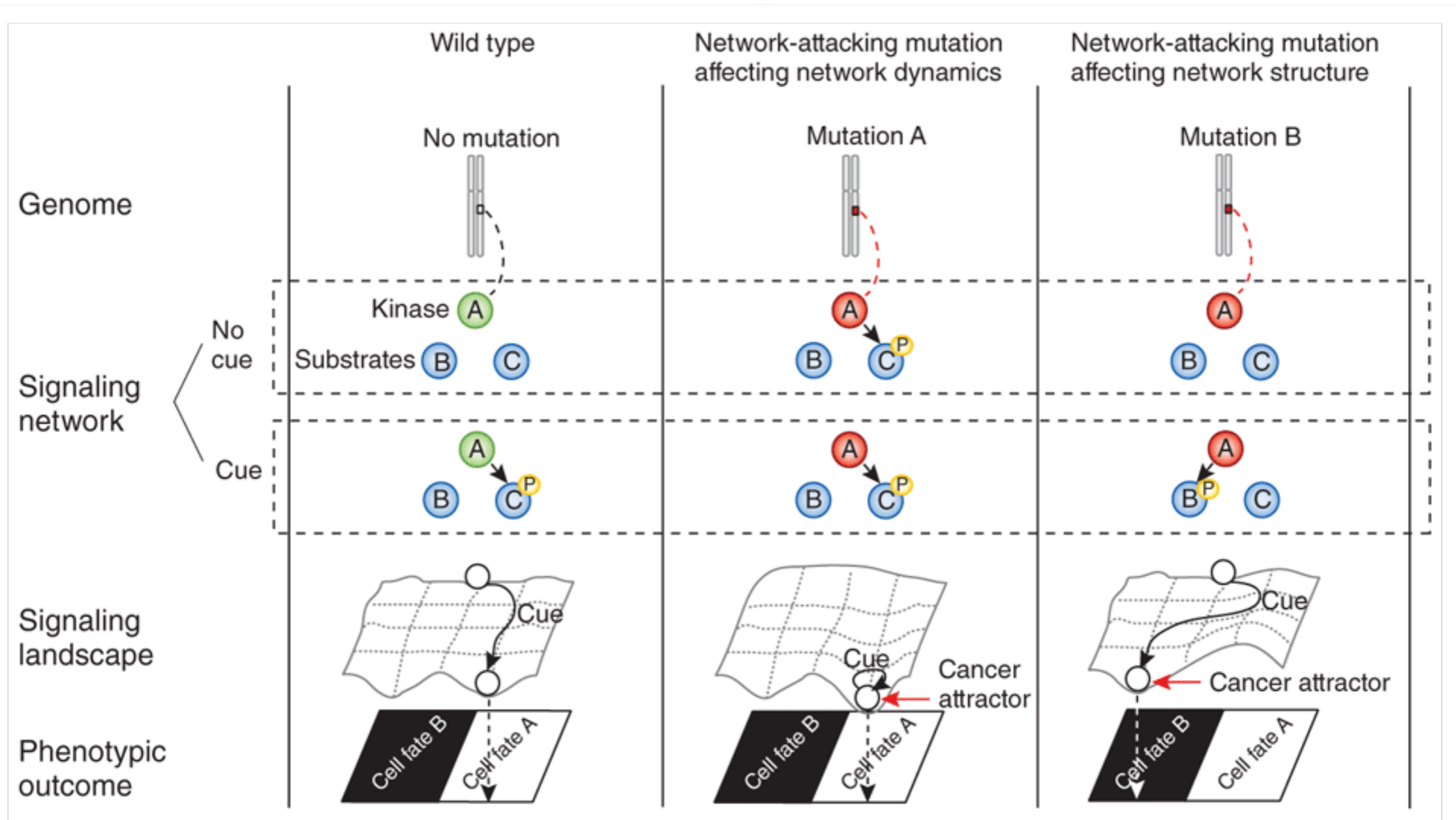
Tyrosine kinase evolution

Noise control in signaling

Cancer Genome Evolution & Kinases
- How do mutations lead to cancer?
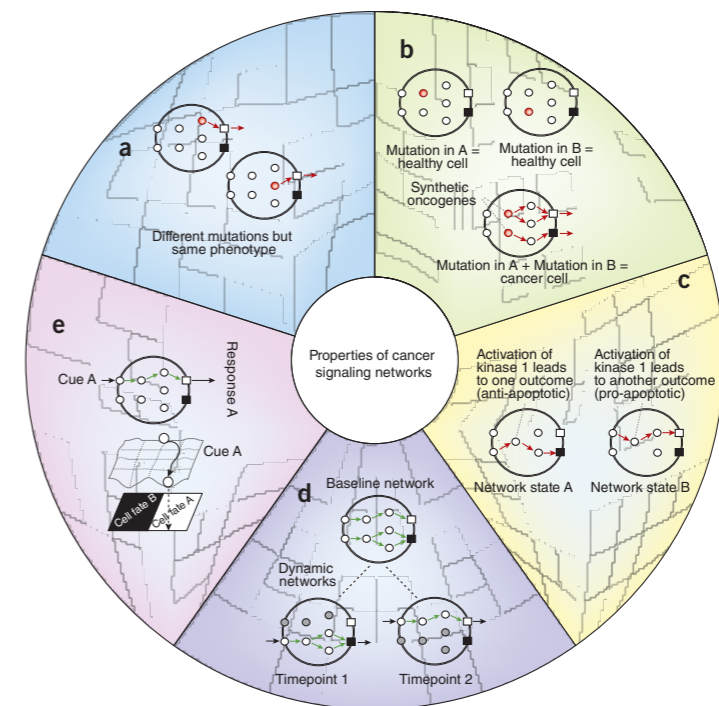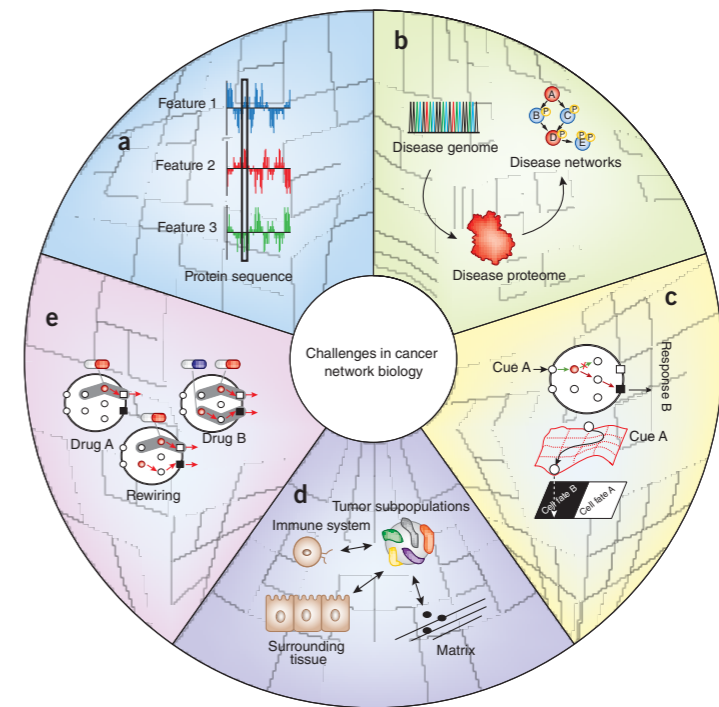
Tumor State Specific Network Medicine

Creixell et al. Nature Biotechnology (2012).

Navigating cancer network attractors for tumor-specific therapy

Pau Creixell[1], Erwin M Schoof[1], Janine T Erler[2] & Rune Linding[1]
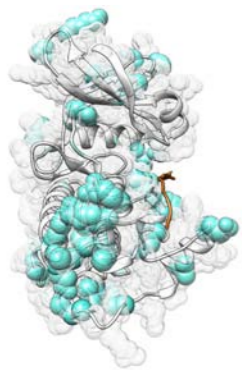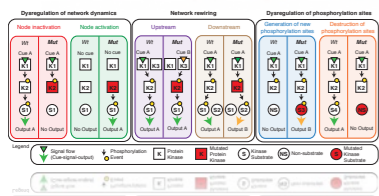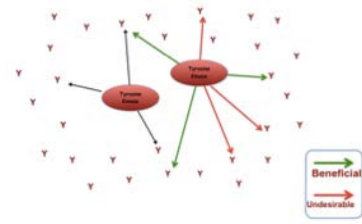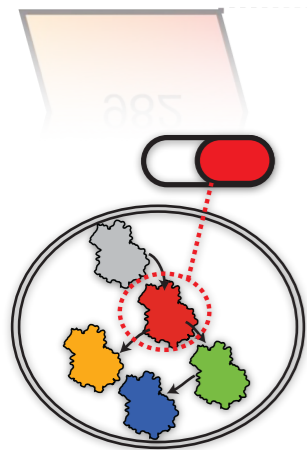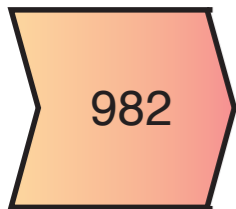
Open Positions in Genome-Scale Proteomics, Modeling, Imaging, Screening and Cancer Biology

Conclusions

I. Tyrosine loss occur in metazoan evolution likely to reduce noise/ enhance **fidelity of signaling systems**

II. Using **comprehensive modeling of kinase mutations** (ReKINect), we have been able to better **interpret** cancer genomes.

III. (With KINspect) We have **found** that substrate specificity is driven by a sparse network of **determinants of specificity** spanning different parts of the kinase domain.

Network-attacking mutations predicted by ReKINect

982

IV. We have **modeled** the effect of mutations and **identified** twice as many **functional mutations** as drivers were known before.

V. We have **deployed** these methods and **identified** a potential **network drivers of resistance and metastasis.**

VI. **Network drug targets more efficacious than single target strategies.** Sunitinib, foretinib and motesanib seem promising candidates for CRC treatment.

Acknowledgements

Kinome Biology Algorithms

Pau Creixell - Erwin Schoof - Jinho Kim (DTU, DK)

Lars Juhl Jensen (CPR, DK) - Mike Yaffe (MIT, USA)

Ben Turk (Yale, USA) - Tony Pawson (SLRI, CA)

Cancer & Tumor Biology

Janine Erler - Tom Cox - Lara Perryman

Alejandro Mayorca (BRIC, DK)

Biological Forecasting

Jesper Ferkinghoff-Borg, James Longden, Xavier Robin (DTU, DK)

Kinase Network Evolution

Chris Tan Soon Heng (CeMM) - Gary Bader (UoT)

Wendell Lim (UCSF) - Tony Pawson (SLRI)

Ruedi Aebersold (ETH) - Neal Rosen (MSKCC)

Mentors

Tony Pawson (SLRI), Mike Yaffe (MIT), Giulio Superti-Furga (CeMM)

Doug Lauffenburger (MIT), Bernhard Palsson (UCSD)

Collaborators

Peer Bork (EMBL, DE)
Rob Russell (UofHD, DE)
Mike Tyers (McGill, CA)
Neal Rosen (MSKCC, USA)
Albert Heck (NPC, NL)
Andrea Califano (CU, USA)
Gerard Manning (Genentech, USA)
Karen Colwill (SLRI, CA)
Luis Serrano (CRG, ES)
Matthias Mann (MPI, DE)
Ruedi Aebersold (ETH, CH)

Industrial Partners

Open Source

Funding

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